REMARKS

Paragraph 1: Specification Amendment

As requested by the Examiner, the specification has been amended to update the status of all related applications. The specification has also been amended to provide the U.S. patent number for the U.S. patent application which has matured into a U.S. patent. No new matter has been added.

Paragraph 2: Rejection of Claims 3-4, 7-8 and 11-12 Under 35 U.S.C. § 112, Second Paragraph

Claims 3-4, 7-8 and 11-12 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In support of the rejection, the Examiner alleges that Claims 3-4, 7-8 and 11-12 are indefinite in the recitation of monoclonal antibody cA2 because its characteristics are not known and cA2 "is merely a laboratory designation which does not clearly define the claimed product". Paper No. 5, at page 2, lines 7-9. Applicant respectfully disagrees with the Examiner's assessment that the use of the term cA2 renders Claims 3-4, 7-8 and 11-12 indefinite.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). If the claims read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, § 112 demands no more. Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 947 (1987).

The specification teaches that cA2 designates a chimeric monoclonal antibody (i.e., a species) which is characterized by the antigen binding variable region of monoclonal antibody A2 and the constant regions of a human IgG1, κ immunoglobulin (see, e.g., page 7, lines 11-13). In addition, significant description of the properties of the monoclonal antibody cA2 (e.g., epitopic specificity and affinity) is disclosed in U.S. Patent No. 5,656,272 (see, e.g., Examples X-XII therein), U.S. Patent No. 5,698,195 (see, e.g., Examples X-XII therein), U.S. Patent No. 5,919,452 and U.S. Application No. 08/192,093 (now U.S. Patent No. 6,284,471; see,

e.g., Examples X-XII therein), each incorporated by reference in Applicant's specification (see, e.g., page 7, lines 3-6). Additionally, the sequences of the antibody are described therein. Thus, when read in light of the specification, a person skilled in the art would find the term "cA2" to be clear and definite. Accordingly, when read in light of the specification, the metes and bounds of Claims 3-4, 7-8 and 11-12 can be determined by a person skilled in the art.

Moreover, it is noted that the term "cA2" is recited in several of the claims of U.S. Patent No. 5,698,195, U.S. Patent No. 5,656,272, U.S. Patent No. 5,919,452 and U.S. Patent No. 6,284,471.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Paragraph 3: Rejection of Claims 3-4, 7-8 and 11-12 Under 35 U.S.C. § 112, First Paragraph

Claims 3-4, 7-8 and 11-12 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner states that:

> The reproduction of monoclonal antibodies is an unpredictable event. The cA2 monoclonal antibodies and the cell line c168A which produces the cA2 monoclonal antibody . . . must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant specification does not disclose a repeatable process to obtain the monoclonal antibody or cell line, and it is not apparent if the monoclonal antibody is readily available to the public.

Paper No. 5, at page 2, lines 18-23. Applicant respectfully disagrees with the Examiner's assessment.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. Exact reproducibility is not required for enablement under 35 U.S.C. § 112, first paragraph. Staehelin v. Secher, 24 U.S.P.Q.2d 1513, 1518 (Bd. Pat. App. Int. 1992). The Court of Appeals for the Federal Circuit has stated that:

> No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.

In re Wands, 8 U.S.P.Q.2d 1400, 1403 (Fed. Cir. 1988). See also M.P.E.P. § 2404.02.

The court also stated in Wands, where a similar rejection was reversed:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. Id. at 1406.

The court in Wands found that screening hundreds of hybridoma clones for a specific antibody did not involve undue experimentation. That is, the court in Wands found that the process of screening hybridomas to select those having the desired property was straightforward with a very high likelihood of success.

The present situation is closely analogous to the facts in Wands. The specification provides considerable direction and guidance and working examples on how to produce and identify chimeric anti-TNF antibodies which would be chemically and structurally similar to those claimed. See the specification, for example, at page 7, lines 3-6, which incorporates by reference information on cA2 to other U.S. patents and patent applications not listed as priority documents (e.g., U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195; U.S. Patent No. 5,919,452; and U.S. Application No. 08/192,093 (filed February 4, 1994; now U.S. Patent No. 6,284,471). U.S. Patent No. 5,656,272, U.S. Patent No. 5,698,195, U.S. Patent No. 5,919,452 and U.S. Patent No. 6,284,471, for example, disclose detailed methods of producing and identifying monoclonal antibodies which would be chemically and structurally similar to those claimed (see U.S. Patent No. 5,656,272, e.g., col. 15, l. 66 to col. 20, l. 46, col. 26, l. 1 to col. 30, l. 47, and Examples I to X; U.S. Patent No. 5,698,195, e.g., col. 16, l. 18 to col. 20, l. 67, col. 26, l. 31 to col. 31, l. 15, and Examples I to X; U.S. Patent No. 5,919,452, e.g., col. 16, l. 1 to col. 20, l. 48, col. 26, l. 6 to col. 30, l. 53, and Examples I to X; and U.S. Patent No. 6,284,471, e.g., col. 15, l. 59 to col. 20, l. 39, col. 25, l. 66 to col. 30, l. 45, and Examples I to X). Thus, given the guidance presented in the specification, antibodies which would be chemically and structurally similar to those claimed can be produced and identified through

routine screening. Therefore, it would not require undue experimentation for one skilled in the art to produce and select antibodies for use in the claimed invention.

Moreover, as stated above, Applicants disclose in the specification that monoclonal antibody cA2 consists of the antigen binding variable region of monoclonal antibody A2 and the constant regions of a human IgG1 κ immunoglobulin (see, e.g., page 7, lines 11-13).

The specification incorporates by reference, for example, at page 7, lines 3-6, the nucleic acid and amino acid sequences of the cA2 light chain variable region and the cA2 heavy chain variable region to other U.S. patents and patent applications not listed as priority documents. U.S. Patent No. 5,656,272, U.S. Patent No. 5,698,195, U.S. Patent No. 5,919,452 and U.S. Patent No. 6,284,471, for example, disclose the nucleic acid and amino acid sequences of the cA2 light chain variable region in Figure 16A and the cA2 heavy chain variable region in Figure 16B. The constant regions of a human IgG1 κ immunoglobulin are readily available in the art.

Accordingly, it would be straightforward for one skilled in the art to produce a monoclonal antibody corresponding to the cA2 antibody, given the guidance presented in the specification (the sequences for the cA2 light and heavy chain variable regions) and what was known to the skilled artisan at the time the subject application was filed (the constant regions of a human IgG1 κ immunoglobulin). No evidence which would support a contrary conclusion has been provided. Thus, there is no basis to question that the skilled artisan, armed with the sequences for the cA2 light and heavy chain variable regions, could produce a monoclonal antibody corresponding to the cA2 antibody.

Reconsideration and withdrawal of the rejection of Claims 3-4, 7-8 and 11-12 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Paragraph 4: Rejection of Claim 5 Under 35 U.S.C. § 102(b) As Being Anticipated by Konno *et al.*

The Examiner has rejected Claim 5 under 35 U.S.C. § 102(b) as being anticipated by Konno *et al.* (*Int. Arch. Allergy Immunol.*, 105:308-316 (1994)), alleging that the cited reference teaches "a method of treating an individual mouse . . . by the administration of a therapeutically effective amount of an anti-TNF-α antibody (see Table 3, in particular)." The Examiner also urges that "by decreasing air overflow in rats made airway hyperresponsive by the administration

of LPS, the prior art teaches treatment of airway inflammation." Paper No. 5, at page 3. The latter statement by the Examiner is not understood.

Applicant respectfully disagrees with the Examiner's conclusion that Claim 5 is anticipated by the Konno *et al.* reference. The Court of Appeals for the Federal Circuit has stated that "[u]nder 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference." Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986) (citations omitted).

Claim 5 relates to a method of treating airway inflammation in an individual comprising administering an anti-TNFα antibody or antigen-binding fragment thereof to the individual.

In contrast, Konno *et al.* disclose treatment of mice with an anti-TNF antibody *prior to* the appearance of inflammatory cytokines in airways and lungs and reported that such treatment inhibited the LPS-induced increase in Mch responsiveness. In particular, Konno *et al.* disclose results from an experiment in which mice were pretreated by intraperitoneal injection with an anti-TNFα polyclonal antibody, and after one hour, were injected intratracheally with LPS, known to be an important stimuli of inflammatory cytokines in airways and lungs (Konno *et al.*, page 310, column 2, paragraph 1). The results, specifically the results in Table 3, are said to indicate that "*pretreatment* of LPS-injected mice with anti-TNF antibody completely blocked LPS-induced increase in Mch responsiveness" (Konno *et al.*, page 311, column 2, paragraph 3; emphasis added). See also Konno *et al.*, page 315, column 2, lines 2-3. As such, Konno *et al.*, at best, disclose treatment of mice with an anti-TNF antibody *prior to onset* of airway inflammation. Accordingly, Claim 5 is not anticipated by the Konno *et al.* reference.

Reconsideration and withdrawal of the rejection of Claim 5 under 35 U.S.C. § 102(b) are respectfully requested.

Paragraph 5: Rejection of Claim 1 Under 35 U.S.C. § 103 As Being Unpatentable Over Konno *et al.* In View Of Shah *et al.*

Claim 1 has been rejected under 35 U.S.C. § 103 as being unpatentable over Konno *et al.* in view of Shah *et al.* (*Clin. Exper. Allergy*, 25:1038-1044 (1995)). In support of the rejection, the Examiner urges that one of ordinary skill in the art would have been motivated to treat asthma with the anti-TNFα taught by Konno *et al.* "because the anti-TNF-α antibody taught by

Konno et al., was effective in reducing airway hyperresponsiveness in LPS treated mice and airway hyperresponsiveness is a characteristic feature of bronchial asthma, as taught by Konno et al." Paper No. 5, at page 4, lines 13-17. The Examiner also urges that one of ordinary skill in the art would have been motivated to treat asthma with the anti-TNFα taught by Konno *et al.* "because Shah *et al.*, teaches TNF-α is an important mediator of asthma and that patients with symptomatic asthma had 20 times greater amounts of TNF-α in their lung fluid then asymptomatic patients and that an anti-TNF-α monoclonal antibody had exciting and dramatic beneficial results in treating rheumatoid arthritis and that since TNF-α plays a fundamental role in both the inflammation and acquired bronchial hyperresponsiveness it raises possible new therapeutic intervention in the treatment of asthma." Paper No. 5, at page 4, lines 17-24. Applicant respectfully disagrees that Claim 1 is obvious in view of the cited references.

As discussed above, Konno *et al.* do not teach or suggest that their anti-TNFα antibody "was effective in reducing airway hyperresponsiveness in LPS treated mice". Rather, Konno *et al.* disclose the administration of anti-TNF antibody to mice *prior to* injection with LPS (see Konno *et al.*, at page 310, column 2, paragraph 1) and report that *pretreatment* with anti-TNF antibody inhibited the LPS-induced increase in Mch responsiveness (Konno *et al.*, page 311, column 2, paragraph 3; and page 315, column 2, lines 2-3). Accordingly, Konno *et al.* do not, and cannot, teach or suggest the treatment of asthma with an anti-TNFα antibody.

Shah *et al.* also do not teach or suggest the treatment of asthma with an anti-TNFα antibody with a reasonable expectation of success. At best, Shah *et al.* invites one of ordinary skill in the art to explore "the possibility of a new type of therapeutic intervention" in the treatment of asthma. An invitation to conduct future experiments to identify a possible method of therapy of asthma is insufficient to provide a teaching or suggestion of the method of therapy with any reasonable expectation of success. As such, Shah *et al.* do not cure the deficiencies of the Konno *et al.* reference.

Accordingly, the cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

Reconsideration and withdrawal of this rejection of Claim 1 under 35 U.S.C. § 103 are respectfully requested.

Paragraphs 6 and 7: Rejections of Claims 1-12 Under 35 U.S.C. § 103

Claims 2 and 6 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Konno *et al.* in view of Shah *et al.* and further in view of U.S. Patent No. 5,698,195 (hereinafter "the Le '195 patent"). Additionally, Claims 1-12 have been rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,698,195 (Le '195) in view of Shah *et al.* and Lukacs *et al.* (*J. Immunol.*, 154:5411-5417 (1995)). Applicant respectfully disagrees with these assessments.

The present invention provides surprising and significant advantages. For example, as set forth in Example 3, antibody therapy with cA2 (infliximab) results in a sustained improvement in both the signs and symptoms of treatment resistant asthma (see specification, Example 3). Furthermore, cA2 therapy has been shown to lead to a decline in asthma symptoms, cessation of nighttime awakening, reduction in steroid use and less reliance on inhaled medication, with improvement beginning within 24 hours (see specification, e.g., page 26, line 14 to page 27, line 1). These specific results would not have been predicted by one of ordinary skill in the art from the teachings of the cited references.

Reconsideration and withdrawal of this rejection of Claims 1-12 under 35 U.S.C. § 103 are respectfully requested.

Paragraph 8: Information Disclosure Statement

As requested, a copy of the Information Disclosure Statement (IDS) filed on January 18, 2002, including page 2 of PTO Form-1449, is enclosed herewith. Entry and consideration of the IDS are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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